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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/473,830	12/28/1999	JEFFREY M. LEIDEN	2844/53802	1518

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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.	Applicant(s)
09/473,830	Leiden et al
Examiner	**Art Unit**
Shin-Lin Chen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED *Mar 24, 2003* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☒ The period for reply expires *6* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *Mar 24, 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see NOTE below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____

3. ☐ Applicant's reply has overcome the following rejection(s): _____

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
Applicants cite Aikawa reference and argue that the claimed method can be used to evaluate regulation and expression of genes in the functioning heart, including hearts in particular disease states (amendment, p. 6). This is

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____

   Claim(s) objected to: _____

   Claim(s) rejected: *24-30, 32, 33, and 35-46*

   Claim(s) withdrawn from consideration: _____

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.

9. ☒ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). *19 & 24*.

10. ☐ Other:

DETAILED ACTION

Continued from Advisory Action:

not found persuasive because the specification fails to provide sufficient description for the use of the claimed method in evaluating the regulation and expression of any gene in a functioning heart including hearts in particular disease states, or in studying a particular promoter activity in cardiomyocytes. No such use has been provided in the specification for a marker gene to assess a particular promoter activity in cardiomyocytes or to evaluate gene expression in the hearts in particular disease states.

Applicants cite Dr. Parmacek's declaration filed 7-8-02 and argue that the claimed method can be used to deliver genes to establish organ model and animal models for human cardiovascular disease (amendment, p. 7, first paragraph). This is not found persuasive because of reasons of record and that the specification fails to provide adequate guidance and evidence for what gene can be delivered to established what type of organ or animal model for what human cardiovascular disease. Since different gene products have different biological function, therefore, various gene expressions in an organ or animal can result in different models for a particular human cardiovascular disease. There is no evidence of record that delivery and expression of a particular gene product in an organ, such as heart, can establish a model for a particular human cardiovascular disease.

Applicants cite Kawada reference and argue that cardiac gene therapy is enabled without undue experimentation and there is no need to demonstrate "clinical efficacy" to establish enablement for the claimed invention (amendment, p. 7). This is not found persuasive because of the reasons of record. As pointed out before, the claims are directed to gene therapy *in vivo* in light of the specification. The state of the prior art of gene therapy *in vivo* was not well developed and was unpredictable at the time of the invention. The specification fails to provide adequate guidance and evidence for the correlation of a desired molecule encoded by various nucleic acid with a particular cardiovascular disease or condition. The specification also fails to provide adequate guidance and evidence whether the desired molecule would be expressed and be present in a sufficient amount at the targeted site such that said desired molecule could provide therapeutic effect for a particular cardiovascular disease or condition in a patient *in vivo*.

Kawada only discloses the use of a particular gene, δ-SG gene to rescue TO-2 hamsters from developing dilated cardiomyopathy (DCM) and to survive longer than control hamsters. However, the specification fails to specifically point out that rAAV-mediated δ-SG gene transfer into the heart can rescue TO-2 hamsters from developing dilated cardiomyopathy (DCM) and to survive longer than control hamsters. In addition, gene therapy *in vivo* using a rAAV vector expressing various gene product, such as anti-sense RNA, contractile protein, a growth factor, an angiogenic factor, a FGF, a VEGF etc., to treat cardiovascular diseases needs to be considered separately because different gene products has different biological functions and pathologies of different cardiovascular diseases differ, and the unpredictable nature of gene therapy *in vivo*.

Doses, schedules, responsive variables, required level and stability of gene expression, and criteria of success all depend on the gene used and the particular cardiovascular disease targeted. Thus, one skilled in the art would require undue experimentation to practice over the full scope of the invention claimed. Although "clinical efficacy" in humans is not necessary for the enablement of the claimed invention, however, sufficient enabling disclosure for the claimed invention is required but the specification fails to do so as discussed above. Therefore, the claims remain rejected under 35 U.S.C. 112 first paragraph.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

S Chen

Shin-Lin Chen, Ph.D.